Communication to the Editor

Increased intensity of *tert*-butoxyl radical emission in 4-chloro-2-methylphenoxyacetic acid (MCPA) synthesis

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Abstract: The important herbicide, 2-methyl-4-chlorophenoxyacetic acid (MCPA) was synthesized by the chlorination of 2-methylphenoxyacetic acid with *tert*-butyl hypochlorite in the presence of methyl *N,N*-dimethylglycinate as a catalyst, giving a high yield and regioselectivity. The reaction was investigated using the spin-trapping technique in electron paramagnetic resonance measurement conditions, with nitrosodurene as a spin trap. Increased intensity emission of the *tert*-butoxyl radical (2.9 times in relation to the starting level) was observed after the catalyst had been introduced into the reaction mixture, indicating a free radical mechanism for the reaction.

Keywords: 4-chloro-2-methylphenoxyacetic acid; 2-methylphenoxyacetic acid; *tert*-butyl hypochlorite; methyl *N*,*N*-dimethylglycinate; *tert*-butoxyl radical; nitrosodurene; spin trapping

1 INTRODUCTION

In recent years considerable attention has been given to regioselectivity in the halogenation of the aromatic nucleus. High regioselectivity in the halogenation of phenols and phenol ethers has been recently reported.[1,2 (and references cited therein)] The commercial herbicide. 4-chloro-2-methylphenoxyacetic acid (MCPA) is manufactured by the chlorination of 2-methylphenoxyacetic acid (MPA) (Fig 1).

The chlorination of MPA may be realized in many ways: eg with gaseous chlorine in organic solvents,[3,4] in an alkaline-aqueous medium,[5] or with hypochlorous acid in aqueous medium.[6] *o*-Chlorination to give 6-chloro-2-methylphenoxyacetic acid and/or cleavage of the phenoxyacetic acid molecule to give the respective chlorophenols may occur as undesired side reactions.

In this paper, we report high regioselectivity in MCPA synthesis by chlorination of MPA with *tert*-butyl hypochlorite (*tert*-BuOCl) in the presence of methyl *N*,*N*-dimethylglycinate (DMGM) as a catalyst. As a free-radical mechanism of chlorination may give rise to high regioselectivity,[7] the investigation of MPA chlorination using a spin trapping technique is also reported. The latter technique involves the reaction of unstable, short-lived free radicals with a spin trap (a nitroso compound or a nitrone) resulting in more stable nitroxyl radicals which are detected by electron paramagnetic resonance (EPR)[8–10] (Fig 2).

2 EXPERIMENTAL

2.1 EPR Spectroscopy

EPR spectra were determined with Bruker ESP 300 E and Radiopan SE spectrometers (9 GHz - X band) and adjusted with a computer program 'Simfonia'. Radical concentration data were obtained by double integration of the EPR signal. Before the EPR measurement, all samples were deoxygenated by passing a nitrogen stream through the solution.

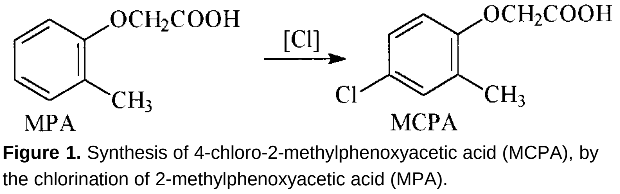

Figure 1. Synthesis of 4-chloro-2-methylphenoxyacetic acid (MCPA), by the chlorination of 2-methylphenoxyacetic acid (MPA).

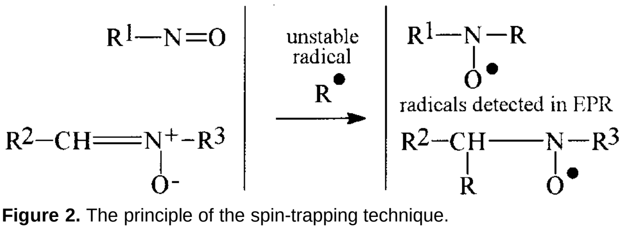

Figure 2. The principle of the spin-trapping technique.

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Table 1. MPA chlorination; laboratory scale; influence of the catalyst (DMGM)

Solvent	Presence of catalyst	Yield of MCPA (%)	Selectivity[a]
Water	+	97	141
Chloroform	+	96	98
Toluene	+	96.5	141
Water	−	84	8.5
Toluene	−	87	13

[a] Defined as a ratio of MCPA to 6-chloro-2-methylphenoxyacetic acid (4-Cl/6-Cl ratio).

2.2 Chemicals

MPA was purchased from Aldrich. *tert*-BuOCl was obtained by chlorination of *tert*-butyl alcohol.[11] Methyl *N*,*N*-dimethylglycinate (DMGM) was obtained by reaction of dimethylamine with methyl chloroacetate.[12] For microscale chlorination in an EPR tube, a DMGM stock solution (0.08547 mmol ml^{-1}) was prepared as follows: 0.1000 g DMGM was weighed into a 10 ml capacity volumetric flask, and toluene was added to 10 ml. The following spin traps: 2-methyl-2-nitrosopropane, α-nitroso-β-naphthol, benzylidene-*tert*-butylnitrone, (4-nitrobenzylidene)-*tert*-butylnitrone, 3,3,5,5-tetramethyl-1-pyrroline *N*-oxide were purchased from Aldrich and applied without further purification. Nitrosodurene was synthesized using known methods.[13,14] 2-Methyl-2-nitrosopropane and benzylidene-*tert*-butylnitrone were also obtained in several steps (yields in parentheses): benzylidene-*tert*-butylnitrone from *tert*-butylhydroxylamine and benzaldehyde (63%),[15] *tert*-butylhydroxylamine from 2-methyl-2-nitropropane (82%);[16] 2-methyl-2-nitrosopropane and 2-methyl-2-nitropropane from *tert*-butylamine (15% and 39% respectively),[17] *tert*-butylamine from *tert*-butylurea (83%);[18] *tert*-butylurea from urea and *tert*-butyl alcohol (30%).[19]

2.3 Preparation of MCPA by chlorination of MPA with *tert*-BuOCl in the presence of DMGM

2.3.1 Preparative scale (Table 1)

MPA (3.3 g, 0.02 mol) and DMGM (0.02 g, 0.17 mmol, 0.85 mol%) were added to an appropriate solvent (Table 1; 60 ml). If water was used as a solvent, the pH was adjusted with sodium hydroxide to 8.5–9. *tert*-BuOCl (2.5 g, 0.023 mol) was added dropwise for 15–20 min at 10–25 °C. The organic solvent was evaporated to dryness *in vacuo*. If water was used as a solvent, the product was extracted into the organic layer using methylene chloride (50 ml). MCPA (m.p 118–119 °C) was obtained in the yields given in Table 1.

2.3.2 Small scale (Table 2)

To a suspension of MPA (0.13 g, 0.78 mmol) in toluene or chloroform (1 ml) in a 5 mm ID tube was added DMGM stock solution (Table 2) and *tert*-BuOCl (0.1 ml), followed by solvent to a total volume of 1.8 ml. The course of the reaction was monitored visually. The poorly soluble MPA disappeared after the times given in Table 2.

2.3.3 EPR measurement conditions (Table 3, Fig 3)

Toluene (1 ml) was placed in the EPR tube. Nitrosodurene (0.127 g, 0.78 mmol), *tert*-BuOCl (0.096 g, 0.885 mmol, 0.1 ml) and MPA (0.13 g, 0.78 mmol) were added and the reaction mixture was diluted tenfold. DMGM stock solution (0.5 ml, 0.0427 mmol, 5.5 mol%) was then added, the tube placed in the spectrometer and the spectrum recorded.

3 RESULTS AND DISCUSSION

3.1 MPA chlorination on a preparative scale

MPA was chlorinated with *tert*-BuOCl in the presence

Table 2. MPA chlorination in EPR tube: rate of the reaction measured as the time of disappearance of MPA precipitate

		Time of disappearance of MPA precipitate	
DMGM stock solution[a] (ml)	Mol DMGM/mol MPA (%)	In chloroform (min)	In toluene (h)
0.02	0.22	90	
0.1	1.1	20–40	24
0.2	2.2	20	10
0.4	4.4		5–6

[a] Concentration of DMGM in the solution – see Section 2.2.

Table 3. MPA chlorination; influence of DMGM addition on increasing *tert*-butoxyl radical emission measured as a *tert*-BDNO concentration

Plot in Fig 3	Reaction mixture	Relative increase of nitroxyl radical (EPR spectrum intensity)
a	Toluene/nitrosodurene/*tert*-BuOCl	1 [def.]
b	Toluene/nitrosodurene/*tert*-BuOCl + MPA	1.3
c	Toluene/nitrosodurene/*tert*-BuOCl/MPA + DMGM	2.9

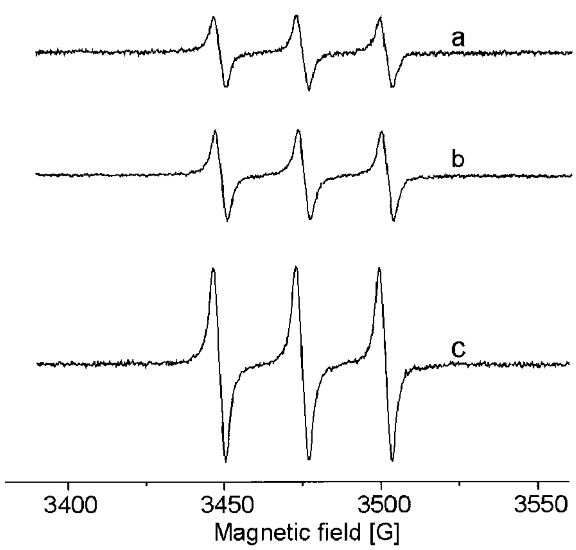


Figure 3. EPR spectra of *tert*-BDNO: (a) starting level – mixture of toluene, nitrosodurene, *tert*-BuOCl; (b) as (a) + MPA; (c) as (a) + MPA + DMGM.

of methyl *N*,*N*-dimethylglycinate (DMGM) as a catalyst.[20] The crucial importance of the catalyst on the yield and especially the selectivity of the process is shown in Table 1.

3.2 MPA chlorination in EPR conditions

3.2.1 Conversion to small-scale conditions

In order to transfer the reaction to EPR measurement conditions, it was performed on a small scale. The rates of reaction in EPR tubes were measured in chloroform and in toluene by the disappearance of the MPA precipitate. The results are presented in Table 2.

3.2.2 EPR measurements

3.2.2.1 General

The reaction was performed in an organic solvent (toluene) using an equimolar amount of a spin trap (nitrosodurene) with the EPR tube placed in the measuring cavity of the EPR spectrometer at ambient temperature. The EPR spectrum was recorded during the reaction for the investigated steady-state system. Two general observations were made:

(i) no adduct of the chlorine radical was detected with any spin trap;
(ii) an EPR spectrum of a nitroxyl radical generated from the *tert*-butoxyl radical was detected in the majority of experiments.

In order to record the best EPR spectrum, the conditions of the EPR tube reaction of MPA chlorination were optimized. The following factors were investigated:

- the choice of a spin trap and a solvent,
- the evaluation of the level of *tert*-butoxyl radical emission,
- the conditions of the experiment (the concentration of reagents in the EPR tube and the sequence of their addition).

3.2.2.2 The choice of spin trap and solvent

The following spin traps were examined: nitroso compounds: nitrosodurene, 2-methyl-2-nitrosopropane, α-nitroso-β-naphthol; nitrones: benzylidene-*tert*-butylnitrone, (4-nitrobenzylidene)-*tert*-butylnitrone, 3,3,5,5-tetramethyl-1-pyrroline *N*-oxide. The most stable spin adduct *tert*-BDNO was detected in the case of nitrosodurene as a spin trap (Fig 4).

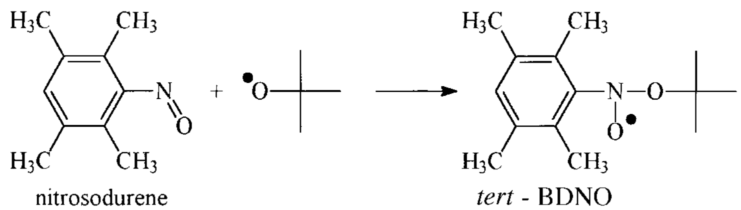
With chloroform as solvent, the EPR spectrum of the radical was observed immediately after placing the EPR tube in the spectrometer, but the concentration of the spin adduct *tert*-BDNO decreased rapidly. In toluene the adduct was more stable. This observation is in accordance with results presented in Table 2, and thus toluene was chosen for the further investigations.

The hyperfine splitting a_N of *tert*-BDNO in toluene is 27.6 G (25.00–25.80 G)[21–25]. The observed higher value of a_N in the reaction mixture indicates an interaction of the spin adduct *tert*-BDNO with MPA and/or its chlorination product. At lower concentrations of MPA, the value will be about 26 G. The influence of the polarity of the various components present in a mixture containing radicals on the a_N value has been reported.[26,27] The typical value of the hyperfine splitting constant a_N for aryl alkoxy nitroxides is in the range 13–15 G [Reference 9, pp 67–68]. The value of almost twice this figure observed for *tert*-BDNO is explained by Sueishi *et al*[21] as being due to the steric hindrance of the 2,6-dimethyl groups in the nitrosodurene fragment, the perpendicular position of this fragment towards the N-O$^\bullet$ group and there being no interaction between unpaired electron and the benzene nucleus.

3.2.2.3 Evaluation of the level of tert-butoxyl radical emission

When the nitosodurene and *tert*-BuOCl were dissolved in toluene in the EPR tube, a constant level of the spectrum of *tert*-BDNO (Fig 3) was observed; this was

Figure 4. *tert*-Butoxy-2,3,5,6-tetramethylphenyl nitroxide (*tert*-BDNO) – a spin adduct of nitrosodurene and *tert*-butoxyl radical.



caused by the homolytic cleavage of *tert*-BuOCl, probably due to the influence of light and temperature.

3.2.2.4 Conditions of the experiment

The best quality EPR spectra were obtained when the starting reagents were diluted and mixed in the sequence: toluene, nitrosodurene, *tert*-BuOCl, MPA, DMGM.

3.2.2.5 Increasing tert-butoxyl radical level

The above results served as a basis for the final evaluation of the level of free radicals in full reaction conditions. As mentioned, the mixture of toluene + nitrosodurene + *tert*-BuOCl yields a low but constant level of *tert*-BDNO. Addition of MPA resulted in an increase of the radical level of about 30%. Introduction of DMGM resulted in a 2.9 times (standard deviation: 0.3) increase of the radical level in relation to the starting level. This is shown in Table 3 and on Fig 3.

4 CONCLUSION

The observed increase of *tert*-butoxyl radical concentration after addition of the catalyst, DMGM, shows the influence of the catalyst on the intensity of homolytic cleavage of *tert*-BuOCl and supports the likely free radical mechanism for the reaction investigated. This may be considered as a reason for the observed high regioselectivity.

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